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STUDY OF A GENERALIZED ERYTHEMA INDUCED BY IODIDES*

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Cutaneous erythema and edema can be elicited in the rat by a variety of substances. Some, like dextran or ovomucoid, induce a reaction localized at the extremities, the snout, and the genital area while others, like compound 48/80 or polymyxin, affect rather evenly the entire skin surface. A feature common to all these agents is that they cause mast cell degranulation in hyperemic areas. Histamine and, in the rat, serotonin are usually released from degranulating mast cells (1–3). Compound 48/80 is well known to induce a decrease in mast cell population as well as in the content of histamine (2, 4) and of serotonin (5, 6) in the tissues of the rat.

The object of this communication is to describe a generalized erythema induced by administration of certain iodine salts, to study the behavior of mast cells under the influence of these iodides and to determine whether or not the presence of mast cells is necessary for the erythematous reaction to appear. The results of these experiments have been described in a preliminary note (7).

MATERIALS AND METHODS

Two hundred and fifty female Sprague-Dawley rats with a mean initial body weight of 115 gm (range: 109 to 119 gm) were divided into 25 equal groups and treated as shown in Table I, II, III and IV. Throughout the experiments the rats were maintained on Purina Laboratory Chow (Purina Co. of Canada) and tap water. The iodides (NaI, KI, NH_4I, Fisher Scientific Co., Montreal, Canada and $MgI_2 \cdot 8H_2O$, Amend Drug and Chemical Co., New York) were administered twice daily. The degree of erythema was assessed semiquantitatively on the basis of an arbitrary scale of 0 to 3, in which 0 = no erythema, 1 = just detectable, 2 = moderate and 3 = maximal. The means of these readings together with the percentage of incidence of erythema are shown in Tables I and II. The experiments were terminated by killing the survivors with chloroform. Portions of tongue, abdominal skin and lower lip were fixed in a mixture of alcohol, formalin and acetic acid for maximal retention of metachromatic material (8), embedded in paraffin, cut at 10 μ and stained with dilute Wright for easy identification of mast cells whose granules become deep blue. The cells were counted with the help of an ocular grid, in the tongue and in the dermis of abdominal skin and cutaneous aspect of lower lip, at a magnification of 400, which produced a field of 0.067 mm^2.

In the first experiment, the individual dose of all iodides (the amount indicated in Table 1) was given in 2 ml of water, by gavage. The animals were killed on the twelfth day, and portions of tongue, abdominal skin and lower lip were fixed for mast cell study. The intensity and incidence of erythema were recorded daily. The means of the readings for three representative days can be found in Table I.

The second experiment (Table II) was undertaken to find out if erythema would appear after subcutaneous or intraperitoneal injections of sodium iodide. Since preliminary experiments had shown that stepwise increase of concentration of iodide enhances the intensity of erythema, the animals were given sodium iodide at the dosage of 0.5 mM for the first four days and of 1 mM on the fifth and subsequent days. Animals of group 2 received the salt by gavage as in the previous experiment, while those of group 3 received it subcutaneously in the back in 0.5 ml of water and those of group 4 intraperitoneally in 1 ml of water. In order to determine if capillary leakage of dye would occur during a period of maximal hyperemia, five controls (group 1) and five iodide-treated rats (group 2) were injected on the seventh day of the experiment with 1.6 mg of Evans blue in 1 ml of water in the jugular vein under light ether anesthesia (9). Twelve hours later all the injected animals were killed and shaved. The remaining hair was removed with a depilator. The other rats were killed on the twelfth day and the usual tissues fixed for histological study.

The aim of the third experiment was to establish if chronic treatment with various iodides would alter the mast cell count of tongue, abdominal skin and lower lip. All the iodides were administered in 2 ml of water by gavage in a similar dosage: 0.5 mM for the first twenty days, 0.75 mM from the twenty-first to the thirtieth day

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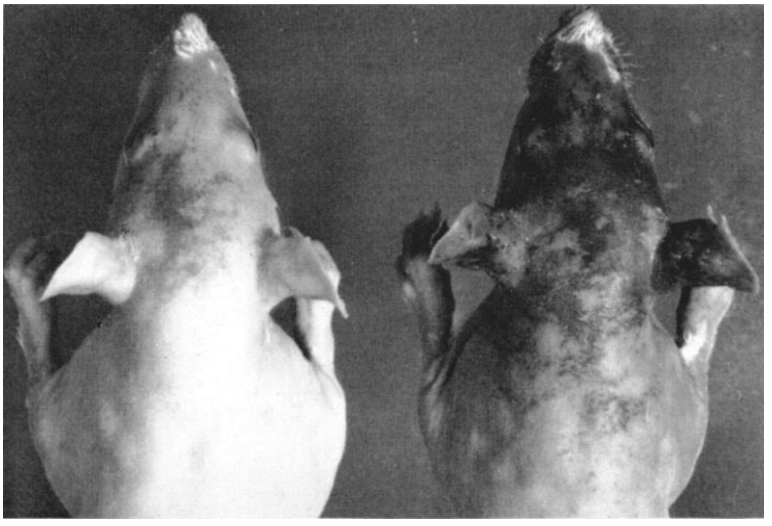

FIG. 1. Rats injected in jugular vein with Evans blue on seventh day of experiment. The control animal (*left*) shows a uniform light gray staining of the skin. Darker spots over calvarium correspond to red capillary bed showing through skin. The sodium iodide treated rat (*right*) shows intense bluing of head, ears, paws, and less marked coloring of whole skin.

and 1 mM from the thirty-first to the fortieth day. The results of the mast cell counts together with their standard errors are listed in Table III.

The fourth experiment was done to ascertain if chronic pre-treatment with ascending doses of compound 48/80 would alter the development of erythema upon subsequent administration of sodium iodide. The animals of groups 3 and 4 (Table IV) were treated for 11 days with increasing doses of 48/80 in 0.2 ml of water administered subcutaneously twice daily starting with 50 μg on the first day with regular increases up to 900 μg on the ninth day. This last dose was then injected twice daily by the same route for the last two days. Starting on the twelfth day, the animals of group 2 and 4 received sodium iodide by gavage at the dose of 1 mM in 2 ml of water. The degree of erythema was assessed daily. The means of these readings with standard error and the percentage of incidence of erythema are shown in Table IV.

RESULTS

Erythema starts on the second day of treatment with iodine salts. The reaction begins with reddening of the base of the ears. It then spreads to the rest of the ears and gradually involves the whole skin. The intensity and duration of erythema are dose dependent (Table I). The only exception was magnesium iodide which induced a weak reaction with as little as 0.125 mM and a more intense erythema with 0.5 mM than with 0.75 mM. Since all the animals were given equimolecular amounts of the various iodides, even of the hydrated magnesium iodide, it is possible that the peculiar effect of the latter and its toxicity (all the rats of group 9 were dead by the seventh day) is related to its containing two iodine atoms in the molecule. Erythema reached a maximum by the fourth day and then gradully diminished. It was finished by the twelfth day except in animals receiving 0.5 mM of sodium iodide (group 2), potassium iodide (group 5), or ammonium iodide (group 11).

As can be seen in Table II, stepwise increase in concentration of sodium iodide displaced the peak of erythema to the seventh day. In all cases the reaction was finished by the twelfth day. At the peak of erythema, a slight and transient edema of the snout and dorsal surface of the paws was present. It ordinarily appeared on the seventh day and was gone the following day. The edema of the ears was more marked and lasted as long as the erythema persisted. The intravenous injection of Evans blue in the animals of group 2 was followed by an intense coloring of the edematous areas and a less marked bluing of the entire skin (Fig. 1). Evans blue at this dosage produced only a faint light gray coloration of the skin

TABLE I

Induction of erythema by various iodine salts

Group	Treatment	mM	Erythema					
			4th D		7th D		12th D	
			Intensity (Scale 0–3)	Incidence %	Intensity (Scale 0–3)	Incidence %	Intensity (Scale 0–3)	Incidence %
1	NaI:	0.125	0	0	0	0	0	0
2		0.5	1.2	70	1.0	70	0.1	10
3		0.75	2.1	100	0.8	60	0	0
4	KI:	0.125	0	0	0	0	0	0
5		0.5	1.6	90	1.0	70	0.1	10
6		0.75	1.9	100	0.4	30	0	0
7	$MgI_2 \cdot 8H_2O$:	0.125	0.2	20	0	0	0	0
8		0.5	2.0	100	0.4	40	0	0
9		0.75	1.3	100	—	—	—	—
10	NH_4I:	0.125	0	0	0	0	0	0
11		0.5	1.2	60	1.3	100	0.7	70
12		0.75	2.0	100	1.8	100	0	0

TABLE II

Effect of route of administration of iodide on erythema

Group	Treatment*	Erythema					
		4th D		7th D		12th D	
		Intensity (Scale 0–3)	Incidence %	Intensity (Scale 0–3)	Incidence %	Intensity (Scale 0–3)	Incidence %
1	Control	0	0	0	0	0	0
2	NaI, P.O.	0.7	70	2.6	100	0	0
3	NaI, S.C.	0.8	80	2.2	100	0	0
4	NaI, I.P.	1.0	80	2.0	100	0	0

* Sodium iodide was given twice a day at the dosage of 0.5 mM from the first to the fourth day of the experiment and of 1 mM thereafter. The salt was administered by gavage (p.o.), subcutaneously (s.c.) or intraperitoneally (i.p.).

of the control rats (group 1). Dye leakage through skin capillaries after treatment with erythema-producing agents is well known (5).

Microscopic examination of tongue, lower lip and abdominal skin after twelve days of treatment with increasing doses of sodium iodide (Table II, groups 2, 3, 4) revealed swelling, vacuolation of the cytoplasm and degranulation of mast cells (Fig. 2), regardless of the route of administration. The extent and severity of mast cell damage were not as great after treatment with 0.75 mM of sodium iodide (Table I, group 3) and gradually decreased with lesser doses so that 0.125 mM (Table I, group 1) induced only minimal changes. The effect of other iodides after twelve days of treatment was similar: the mast cell damage was generally proportional to the dose of salt used.

After twenty days of treatment with sodium iodide (Table III) erythema was no longer present. The subsequent increases in dosage, to 0.75 mM and finally to 1 mM, were not followed by reappearance of erythema although the same doses of iodide, given to untreated rats of similar weight, invariably produced

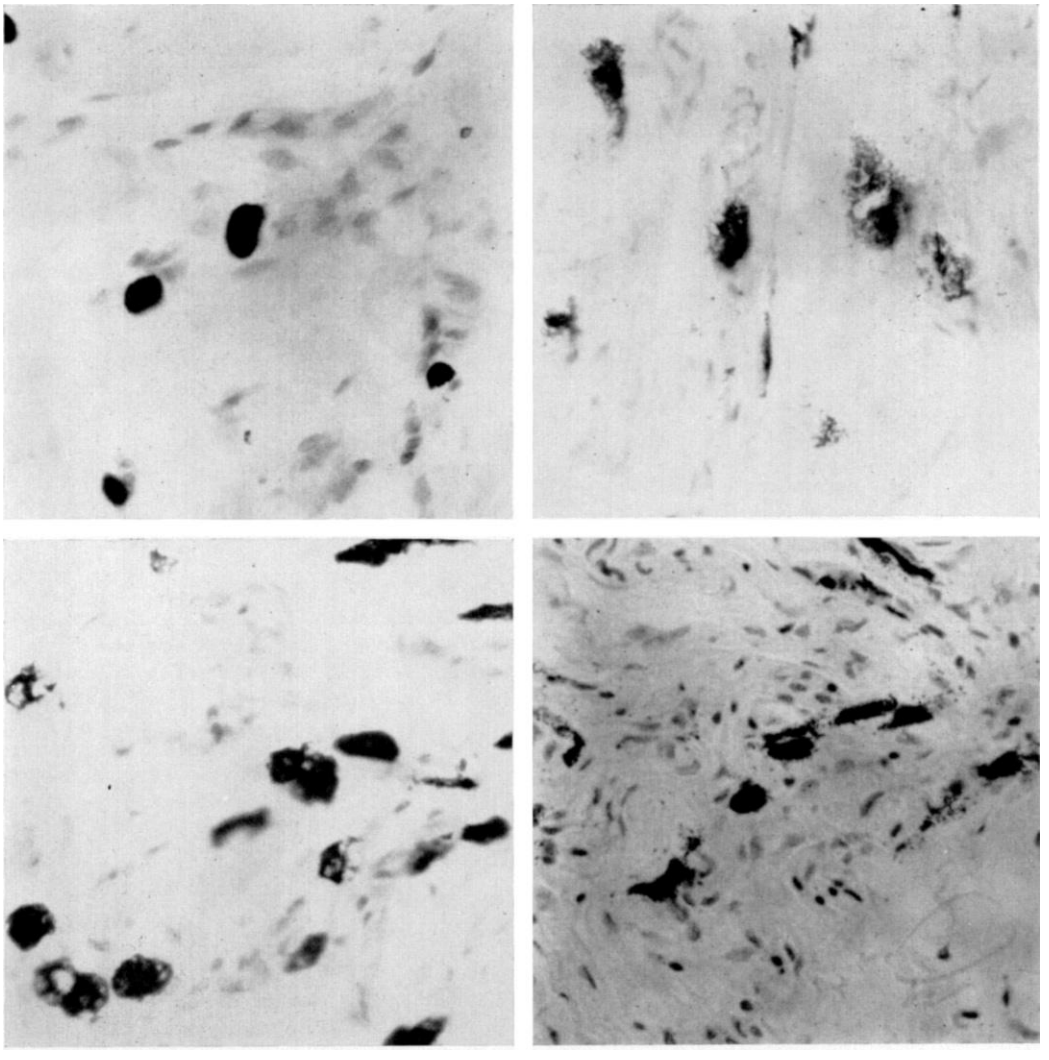

FIG. 2. *Top left:* Section of tongue of normal rat: Mast cells appear as dark, well delimited dots on a light background. *Top right:* Section of tongue of iodide-treated rat (sodium iodide by gavage twice a day for 12 days; ½ mM from the first to the fourth day and 1 mM thereafter). Mast cells are hazy because of peripheral dispersion of granules and the presence of fine vacuoles in their cytoplasm. *Bottom left:* Section of lower lip of iodide-treated rat: Mast cells are swollen and contain some vacuoles. *Bottom right:* Section of abdominal skin: Mast cells in dermis are swollen. Some are surrounded by granules. Dilute Wright × 400.

erythema (10). Thus chronic treatment with relatively low doses of iodide precludes the occurrence of erythema upon exposure of the animals to higher concentration of the salt.

Forty days of treatment with increasing doses of various iodides decreased the dermal mast cell population of abdominal skin by 42% to 65% (Table III), depending on the salt used. The diminution of the number of mast cells in the dermis of the lower lip and in the tongue was not as important, varying between 39% and 43% in the former and between 24% and 46% in the latter. Of the remaining mast cells, only a few were degranulated, and most assumed a normal appearance.

The rats injected with ascending doses of 48/80 (Table IV, groups 3 and 4) showed erythema and edema of the extremities. These effects, generally attributed to liberation of

TABLE III

Effect of chronic treatment with iodine salts on the mast cell population of some tissues

Tissue	Treatment*	Number of fields	Total number of mast cells	Average/field
Tongue	Control (7)†	1169	7723	6.6 ± 0.80
	NaI (8)	1339	4950	3.6 ± 0.20
	KI (4)	833	3618	4.3 ± 0.18
	$MgI_2 \cdot 8H_2O$ (4)	925	4677	5.0 ± 0.18
	NH_4I (3)	600	2853	4.7 ± 0.10
Abdominal skin	Control (7)	293	1975	6.7 ± 0.72
	NaI (8)	283	1099	3.9 ± 0.31
	KI (5)	201	564	2.8 ± 0.25
	$MgI_2 \cdot 8H_2O$ (4)	161	394	2.4 ± 0.33
	NH_4I (3)	140	421	3.0 ± 0.17
Lower lip	Control (7)	257	3217	12.5 ± 0.96
	NaI (7)	320	2431	7.6 ± 0.45
	KI (5)	200	1547	7.7 ± 0.55
	$MgI_2 \cdot 8H_2O$ (4)	167	1204	7.2 ± 0.70
	NH_4I (4)	164	1266	7.7 ± 0.14

* The iodine salts were given twice a day at the following doses: 0.5 mM for the first twenty days, 0.75 mM from the twenty first to the thirtieth day and 1 mM from the thirty first to the fortieth day.

† Parentheses enclose the number of animals used for mast cell count.

TABLE IV

Effect of pretreatment with 48/80 on iodide-induced erythema

Group	Pretreatment*	Treatment†	Erythema	
			Intensity (Scale 0-3)	Incidence %
1	None	None	0	0
2	None	NaI	2.5 ± 0.18	100
3	48/80	None	0	0
4	48/80	NaI	0	0

* Compound 48/80 was given from the first to the eleventh day of the experiment.

† Sodium iodide was administered at the dosage of 1 mM starting on the twelfth day of the experiment. Reading of erythema was done on the seventeenth day.

endogenous vasoactive amines, gradually decreased so that hardly any visible sign of their liberation could be detected even after the last large doses of 48/80. All animals of group 2 (Table IV) that were treated with sodium iodide developed a generalized erythema which reached a maximum on the seventeenth day of the experiment and gradually decreased thereafter. In animals that were pre-treated with 48/80 (group 4), subsequent administration of sodium iodide did not produce erythema at any time.

DISCUSSION

Since the erythema induced by administration of various iodides is accompanied by mast cell damage and eventually by a decrease in the mast cell population of tongue, abdominal skin and lower lip, it is possible that peripheral vasodilatation is related to the release of vasoactive amines from mast cells. The absence of erythema in the 48/80-treated rats gives support to this hypothesis. Decrease of the mast cell population and of the histamine and serotonin content of tissues by 48/80 would prevent the occurrence of erythema upon subsequent treatment with sodium iodide by removing the cause of the peripheral effect of the iodide. The absence of erythema in rats chronically treated with sodium iodide upon exposure to a higher concentration of the iodide could be interpreted in the same manner.

Several mechanisms whereby iodides could influence mast cells are possible. Iodides could primarily influence blood vessels since it has

long been known that topical application of iodine on a mucous membrane is followed by vasodilatation (11). Similarly, administration of iodine to the whole animal or limb and organ perfusion allegedly induces a variable degree of vasodilatation depending on the species used and on various other factors 12). If this is correct, mast cell degranulation and possibly subsequent histamine or serotonin release would be secondary phenomena related to osmotic and other environmental changes in connective tissue. The passive breakdown of mast cells as a result of vasodilatation and edema is well documented (13, 14). This hypothesis is difficult to reconcile with the fact that previous chronic treatment with 48/80 or iodide prevents the occurrence of erythema upon subsequent administration of iodide. Another possibility arises from the fact that an anaphylactic shock has been produced in the guinea pig by injection of a mixture of iodine and guinea pig serum (15). Also the occurrence of periarteritis nodosa as well as of arthralgia and eosinophilia in a patient suffering from iodine intoxication has led Rich to postulate hypersensitivity as the cause of these phenomena (16). It is thus possible that erythema and mast cell degranulation, following iodine intoxication in the rat, could have a similar basis. A third possibility stems from radioautographic studies which showed that the injection to rats of carrier free sodium iodide^{131} or sodium iodide^{125} produces a selective concentration of radioactivity in mast cells of skin and muscle even after thyroidectomy or treatment with propylthiouracil (17). The fact that no mast cell damage was reported after injection of tracer doses of iodide is in agreement with our findings that even as high a dose as 0.125 mM of sodium iodide does not induce erythema and produces only minimal mast cell disruption. This observation, however, raises the possibility that the breakdown of mast cells in skin and tongue following administration of large doses of iodides results from the selective accumulation to toxic levels of iodide in these cells. If this assumption is correct, mast cell degranulation and erythema are merely a special manifestation of iodine toxicity and do not depend on hypersensitivity reactions or on primary vascular involvement.

Iodine has been extensively used in clinical medicine for such diverse ailments as coughs, syphilis and thyrotoxicosis. It has been administered to patients in radiological contrast substances, in proprietary asthma tablets, in syrups, and in the form of Lugol's solution or compound solution of iodine. The relatively infrequent toxic reactions to iodine in man are characterized by pruritus, maculopapular cutaneous erythema, pharyngeal erythema, conjunctivitis, coryza, fever and eosinophilia (16, 18–20). Since eosinophilia has been linked with release of histamine (21), the possibility arises that some of the effects of iodine intoxication in man, depend, at least partly, on mast cell damage and liberation of histamine.

SUMMARY

Administration of large doses of various iodides to rats is followed by a generalized erythema accompanied by mast cell degranulation and eventually by decrease in the mast cell population of various tissues. This reaction is prevented by previous treatment with 48/80 or iodide.

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